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Genes, genetics & genomics – do they pose an existential threat to Critical illness as we know it?

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Critical illness…..

Born in the 1980s…

…and still there?

"Genomic sequencing is like the internet back in the 1980s"

Professor George Church – Professor of Genetics Harvard Medical School

The Guardian 11 February 2018

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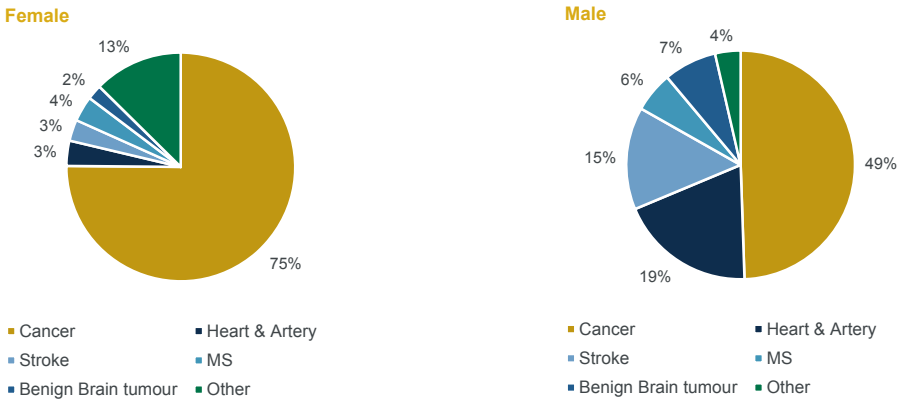
Claims



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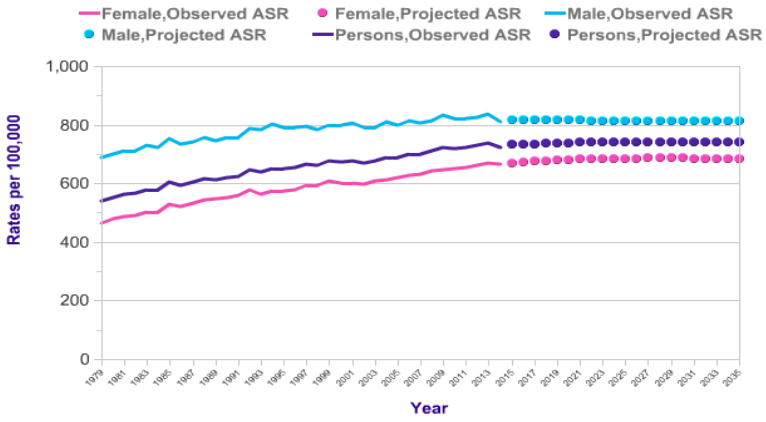
Pricing assumptions



All cancer incidence to 2035- Source CRUK

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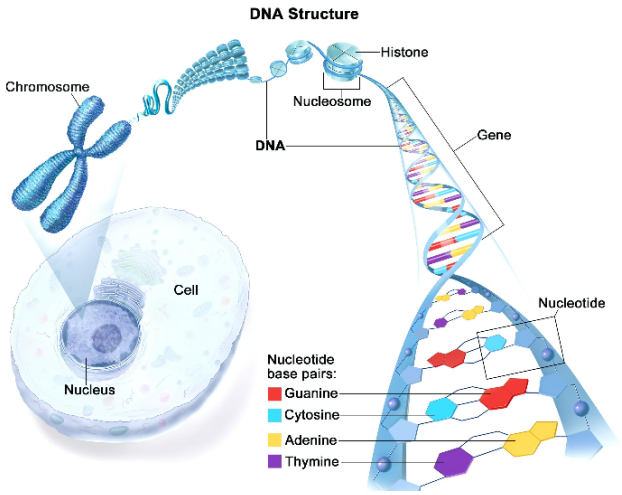
Genetics – by a dummy



- Genome – all hereditary genetic material
- Chromosome – segments or sections of DNA, proteins and RNA in cells
- DNA is made up of only four repeating building blocks we call nucleotides. These nucleotides are nicknamed A, T, G and C (for Adenine, Thiamine, Guanine, and Cytosine). There are approximately 3 billion nucleotides in the human genome
- Gene – segments of 5' to 3' DNA strands (promotors, exons, introns) WE have around 22,000 genes
- Allele – one of 2 or more variants of each gene (two of which are inherited from parents
- Genotype - coded information two types
  - Homozygote: same allele AA, aa
  - Heterozygote: different alleles Aa
- Phenotype a physical manifestation of a characteristic
  - Dominant trait – expressed
  - Recessive: not expressed
    - autosomal recessive must get two abnormal copies to get disease
    - x linked recessive – females are carriers so only males can get disease

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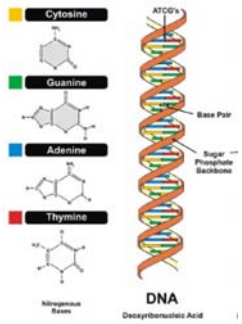
What causes genetic mutation?



Mutation

1. Germline or Inherited mutations
2. Somatic mutations not inherited.
   - Environmental influences – ionising radiation, dietary factors, smoking, viral damage etc.
   - And/or accumulated damage from above over time –'ageing'

Polymorphism

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Genetic disease

- Any disease that is caused by an abnormality in a person's genome; ***the genome is the entirety of their genetic make-up***

Types of 'genetic disease'

- Multi factorial, complex or polygenic
- Single gene, 'Mendelian' or monogenetic ('classic genetic diseases')
- Chromosomal
- Mitochondrial

Common

Rare

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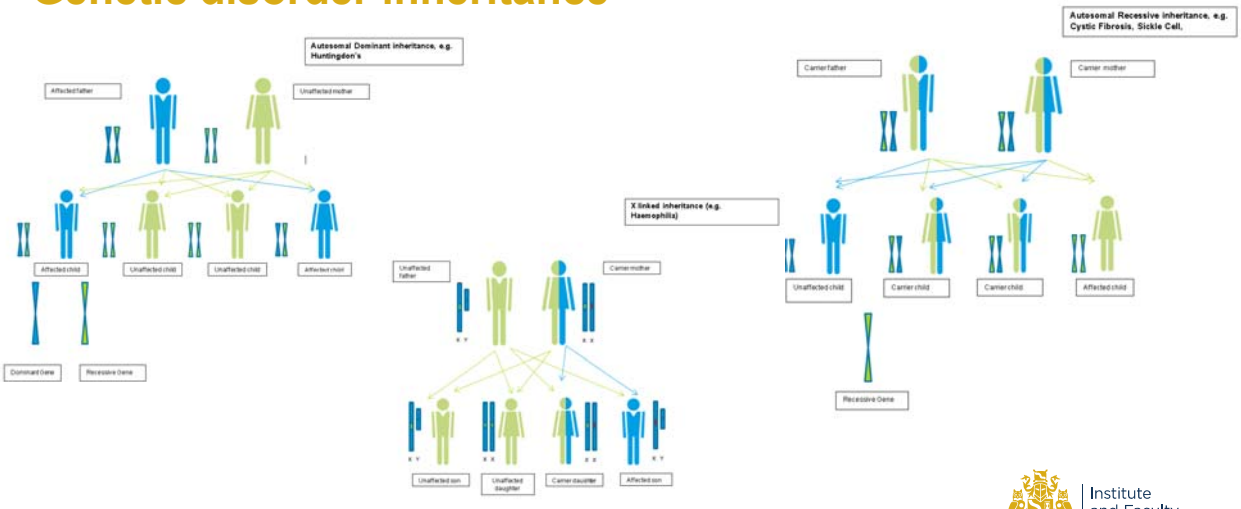
Genetic disorder inheritance



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Genetic testing

- Diagnostic testing
- Predictive and pre-symptomatic genetic testing
- Carrier testing
- Prenatal testing
- Pre-implantation genetic testing
- New born screening
- Pharmacogenetic testing
- Research genetic testing

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Whole Genome Sequencing

- Genomics v genetics
- Human genome finally mapped in 2003 at a cost of $3bn
- Currently now $1k aim to be $100 in next 10 years
- New sequencing allied to massively increased computational power means we can now look at an whole 6.4 billion letters in a persons genome
- SNP (single nucleotide polymorphism) is a type of mutation.
- rs334 (A) V rs334 (T) - Sickle Cell

The Guardian

'We are all mutants now': the trouble with genetic testing

With so many unknowns in our DNA, using genetics in medical testing doesn't always bring the answers - sometimes it brings only doubt. By

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What's happening with WGS

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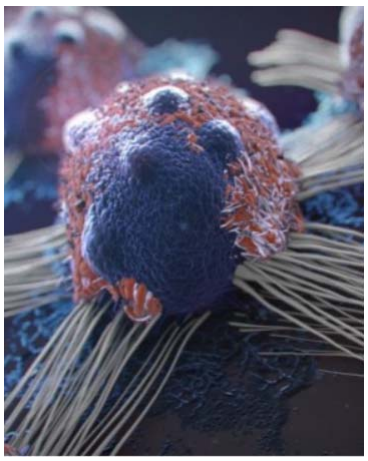
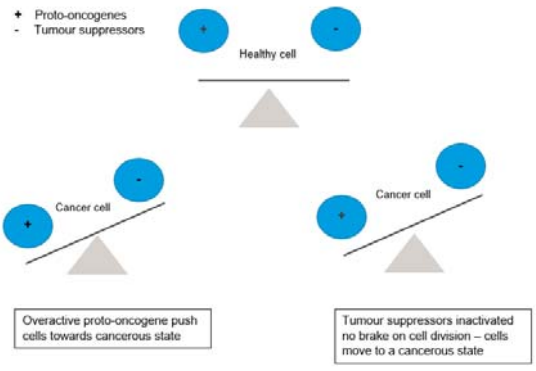
Cancer genetics a basic overview





Derived from Carey, N. 'The epigenetics revolution' , 2011

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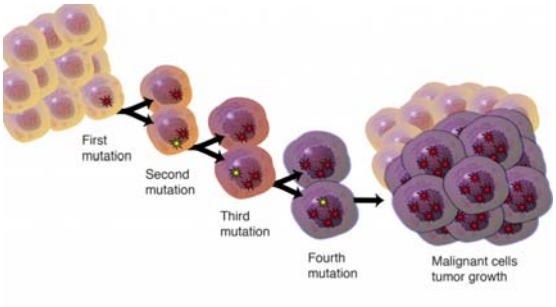
Cancer – genetics



- Not only factor
- Cells can proliferate but remain structurally normal
- Need other defects to accumulate defects need to be passed from ancestor or mother cell to descendent or daughter cells
- Not only that you have two copies of tumour suppressor genes (they're carried on autosomes) need both to be 'switched off'
- 'Your genetics loads the gun your lifestyle pulls the trigger' Mehmet Oz

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Cancer genomic

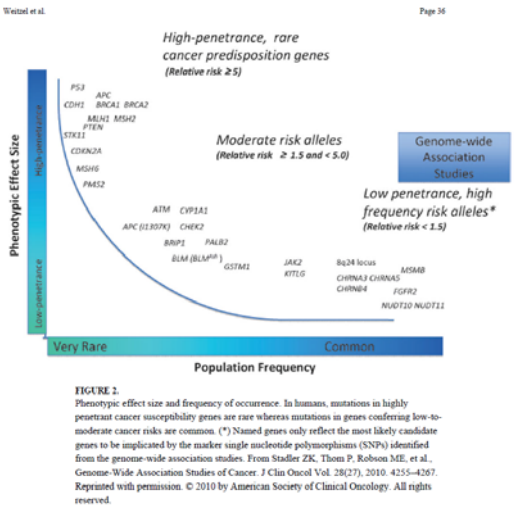

FIGURE 2.
Phenotypic effect size and frequency of occurrence. In humans, mutations in highly penetrant cancer susceptibility genes are rare whereas mutations in genes conferring low-to-moderate cancer risks are common. (*) Named genes only reflect the most likely candidate genes to be implicated by the marker single nucleotide polymorphisms (SNPs) identified from the genome-wide association studies. From Stadler ZK, Thom P, Robson ME, et al. Genome-Wide Association Studies of Cancer. J Clin Oncol Vol. 28(27), 2010. 4255–4267. Reprinted with permission. © 2010 by American Society of Clinical Oncology. All rights reserved.

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Threats to CI

- Treatment
  - incremental survival improvements – short to medium
  - revolutionary changes, individualised and tailored to your genomic profile
- Diagnostics, screening and prediction
- Patient/consumer expert armed with knowledge of their health and rights
- 'Conditions race' more illnesses covered, often rare, with more generalised less specific definitions

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The present and not so distant future
Personal Genomic Testing (PGT) services

- Direct-to-consumer personal genomic testing has become an affordable reality
- Privately available gene testing available for sometime. Motivated in family history research and popularised by

23andMe ancestry

- Enables citizens/consumers to 'cut out the middleman' (democratisation or its it part of 'anti-expert' cultural trend?) and own and interpret their own DNA sequence data and are able to potentially effect diagnostic, therapeutic and preventive actions
- October 2017 Researchers in Manchester University NHS trust developed a new test identify 18 SNPs indicative of a breast cancer risk in women NOT carrying BRCA1/2

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Personal Genomic Testing (PGT) services ..2

Risks to insurers

- Reinforce and embed knowledge dissymmetry
- Can't rely on 'misrepresentation'… because of

'Genetic exceptionalism'

- Moratorium – UK, or legislation – USA GINA act, regulations - EU

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Diagnosis – Liquid Biopsies

- Cancer is diagnosed by histopathology (take a tissue sample and analyse it)….not anymore it seems
- New non-invasive test 'liquid biopsy' techniques targeted at finding circulating tumour cells (CTCs), circulating tumour DNA (ctDNA) or microRNA/exosomes in the blood.

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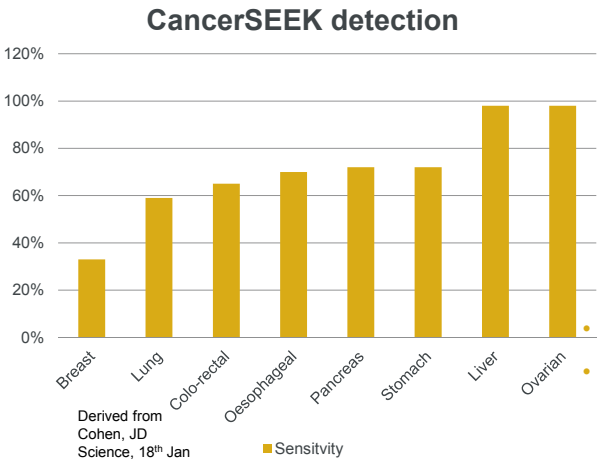
Liquid biopsies..2



- Only detected 43% of stage 1 cancer.
- Efficacy mixed depending on type but sensitivity good for difficult to diagnose tumour

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Genetic anti-cancer therapies

- Efficiency therapy
- Immunotherapy - boost the body's natural ability to attack cancer cells
- Triggering programmed cell death or apoptosis
- Altered viruses – using genetically modified viruses to kill cancer

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Personalised cancer therapy

- However….efficacy at the moment remains modest. In a recent report all cancer patients referred for genetic analyses only 3 to 13 % had treatments selected on the basis of their individual genomic tests[1]
- Why? Simply put cancer is molecularly complex, not only does it evolves or mutates rapidly cancer cells within the same tumour (not to mention metastatic offshoots) can differ. Puts any treatment options under pressure.

[1] Tannock IF et al. Limits to Personalised Cancer Medicine. The New England Journal of Medicine. September 29, 2016, 375;13 pp 1289

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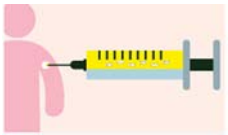
Treatment - CRISPR

- CLUSTERED REGULARLY INTERSPERSED SHORT PALINDROMIC REPEATS
- ‘True genetic engineering ’ or more accurately gene editing
- Single gene and/or SNP repair
- What about more complex disease like cancer?



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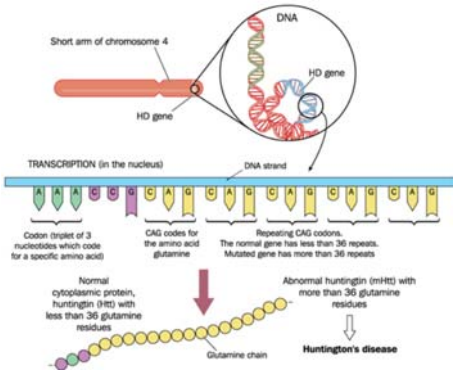
New frontiers - curing the incurable

- Huntingdon's -IONIS-HTT(Rx) works by effectively silencing the defective huntingtin gene.
- Cystic Fibrosis – missing 3 nucleotides in DNA of region in chromosome 7
- Sickle Cell - LentiGlobin BB305 vector - case study report of boy in France cured. In sample cells in lab – using CRISPR mistake corrected
- Blindness - Luxturna, aims to correct a mutation responsible for a range of retinal diseases that make people gradually go blind. In human tests, the treatment has restored vision for more than two dozen patients who were losing their sight
- Multiple sclerosis - immunotherapy uses a virus to deliver a liver-targeted gene that expresses full-length myelin oligodendrocyte glycoprotein (MOG) in liver cells. This is MOG, a myelin sheath protein, causes the production of regulatory T-cells, which inhibit the immune response that otherwise would attack the patient's myelin sheaths.



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Professor George Church – Turning Back Time to End Age-related Diseases

Victor Bjoerk and Steve Hill August 1, 2017 1

- Interesting that DNA is biological data right?
- All of these are backed by powerful information technology

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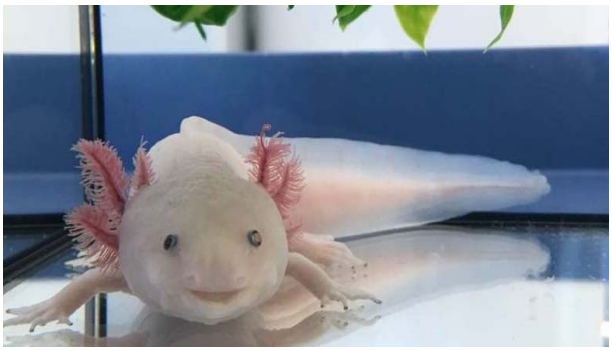
Not so distant future



- An Axolotl
- Scientists mapping the genome of this Mexican Salamander (it's an amphibian)
- Why? Its genome is enormous 32 million base pairs (10x bigger than humans) it can regrow limbs if severed and repair spinal cords and retinal tissue

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…..And so? A threat to the existence of CI..

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…perhaps not [yet] - Evolution and opportunity

- Prognosis v Diagnosis

- Treatment costs

"*Gene therapy is now available but could cost millions over a lifetime say scientists*" The Independent 2 April 2018

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…what about the past?





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